

ORGANIC CHEMISTRY | RESEARCH ARTICLE

Concise synthesis of substituted meridianins

Jenifer T.A. Vijay, Nandeesh K. Nagalingaiah, Sandhya C. Nagarakere, G.P. Suresha, Rangappa S. Kanchugarakoppal and Mantelingu Kempegowda

Cogent Chemistry (2015), 1: 1083068



Received: 10 March 2015
Accepted: 06 August 2015
Published: 22 October 2015

*Corresponding authors: Rangappa S. Kanchugarakoppal and Mantelingu Kempegowda, Department of Studies in Chemistry, Manasagangothri, University of Mysore, Mysore 570006, India
E-mails: rangappaks@gmail.com (Rangappa S. Kanchugarakoppal); kmantelingu@yahoo.com (Mantelingu Kempegowda)

Reviewing editor:
George Weaver, University of Loughborough, UK

Additional information is available at the end of the article

ORGANIC CHEMISTRY | RESEARCH ARTICLE

Concise synthesis of substituted meridianins

Jenifer T.A. Vijay¹, Nandeesh K. Nagalingaiah¹, Sandhya C. Nagarakere¹, G.P. Suresha¹, Rangappa S. Kanchugarakoppal^{1*} and Mantelingu Kempegowda^{1*}

Abstract: A mild and versatile method for the efficient construction of heterocyclic framework of meridianins from simple precursors has been devised. The strategy involves the assembly of the pyrimidine ring utilizing the nucleophilicity of mono-thio-1,3-diketone formed by thioacylation at the C-3 in the indole ring.

Subjects: Medicinal & Pharmaceutical Chemistry; Natural Products; Organic Chemistry

Keywords: meridianin; monothio-1; 3-diketone; thioacylation

1. Introduction

Indole happens to be the most interesting molecule which the chemists have explored time and again. Its occurrence in natural products has intensified its scope for application in various fields of research. Through the years, work on indole moiety was mostly concentrated on the variations effected at C-3 position, as indole undergoes readily electrophilic substitution (Sundberg, 2010). Literature reports showed an interesting class of indole-based marine alkaloids with pyrimidine ring at the C-3 position, and these include Variolins (Trimurtulu et al., 1994), Psammopemmins (Butler, Capon, & Lu, 1992), Hyrtinadine A (Endo, Tsuda, Fromont, & Kobayashi, 2007), Aplicyanins (Reyes et al., 2008), and Meridianins (Herna et al., 1998; Seldes, Rodriguez Brasco, Hernandez Franco, & Palermo, 2007) (Figure 1).

Among these tethered biheterocycles, meridianins are being studied for their potent kinase inhibition, as they inhibited CDKs, GSK-3, PKA, and other protein kinases in low micromolar range (Gompel et al., 2004). Meridianins (A–G) are a family of alkaloids isolated from the South Atlantic tunicate



Rangappa S. Kanchugarakoppal

ABOUT THE AUTHORS

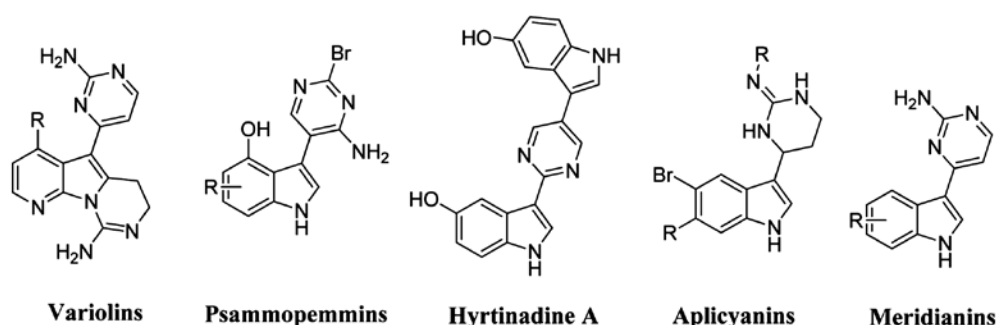
Our research group is headed by Prof. Rangappa S. Kanchugarakoppal, PhD, DSc, FRSC, FNAsc, the current Vice-Chancellor of University of Mysore. He is the recipient of several prestigious awards. He has 400 research papers in National and International peer-reviewed journals and has over 2,200 scientific citations as of 2015. He has guided 50 PhD students and 7 are working under him.

Dr. Mantelingu Kempegowda, (Assistant Professor in Chemistry, University of Mysore), one of the PhD students of Prof. Rangappa S. Kanchugarakoppal is the other corresponding author of this paper. He is also the recipient of Merck Millipore India Innovation Award 2012. The main focus of our research group is to develop simple and efficient synthetic strategies for heterocyclic compounds. In this work, dithioesters are used as a precursor for the construction of 4-amino pyrimidine ring at the C-3 in the indole ring leading to the synthesis of substituted marine alkaloid, Meridianin.

PUBLIC INTEREST STATEMENT

People have always looked up to Mother Nature for solutions to cure ailments and diseases. Usually, the secondary metabolite, be it plant or animal, are extracted and screened for its medicinal properties. The isolated natural products are chemically analyzed and characterized. To formulate the syntheses of these natural products in the laboratory has been challenging task to the chemists. Interestingly, even marine animals are also exploited and among them is South Atlantic tunicate *Aplidium meridianum*. The alkaloids, Meridianins (A–G), isolated from the tunicate are known for their potent kinase inhibition, inhibiting CDKs, GSK-3, PKA, and other protein kinases in the low micromolar range. In this context, we have devised a route for the synthesis of substituted meridianins from simple dithioesters.

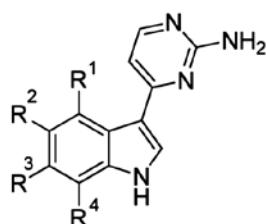
Figure 1. Indole-based marine alkaloids.



Aplidium meridianum, containing a 2-aminopyrimidyl ring at C-3 position with variations at 4-, 5-, 6-, and 7-positions of indole ring (Figure 2).

Owing to its unique structure and biological activity, several methods have been proposed for the synthesis of most of the members of the family as well as syntheses of numerous analogs. Basically, the structure of meridianins could be achieved by three main routes; one is by introducing 2-amino pyrimidine to indole by Suzuki coupling (Jiang & Yang, 2000), and second is by constructing a 2-aminopyrimidine by Bredereck synthesis of indole-enaminone with guanidine (Agarwal, Dathi, Saifuddin, & Kundu, 2012; Fresneda, Molina, & Bleda, 2001; Fresneda, Molina, Delgado, & Bleda, 2000; More, Jang, Hong, & Lee, 2014; Sperry, 2011). The third route being the synthesis from monocyclic alkynes via Sonogashira coupling (Karpov, Merkul, Rominger, & Müller, 2005; Tibiletti et al., 2010) and Cacchi indole synthesis (Walker, Czyz, & Morris, 2014). The acid-mediated direct alkenylation of indoles with α -oxo ketene dithioacetals and subsequent condensation with guanidine is the first and only report to use a sulfur synthon (Yu & Yu, 2009). Furthermore, substitution on C-5 position of the 2-amino pyrimidine ring by various aryl groups has shown significantly lesser cytotoxicity toward PA 1 cells (Akue-Gedu et al., 2009), and substitution on indole ring at C-5, C-6, and C-7 has produced compounds with potent and selective inhibition of Dyrk1A indicating potential of these compounds to emerge as lead candidates for neurodegenerative diseases (Bharate, Yadav, Battula, & Vishwakarma, 2012). Most of the reported methods make use of transition metal, expensive reagents and reactants, and require maintaining certain reaction conditions. Additionally, the variation in the substituent can be decided with dithioester before the formation of meridianin analogs, rather than adding more steps in introducing substituent to meridianin. Inspired to overcome these challenges and also as our research being mainly based on construction of heterocycles using dithioesters and its derived synthons, we attempted to devise a method for the synthesis of meridianin analogs wherein the reactants are easily synthesized and in addition the number of reactants and steps are reduced.

Figure 2. Meridianins (A–G).



- Meridianin A (1) $R^1=OH$, $R^2=R^3=R^4=H$
 Meridianin B (2) $R^1=OH$, $R^2=R^4=H$, $R^3=Br$
 Meridianin C (3) $R^1=R^3=R^4=H$, $R^2=Br$
 Meridianin D (4) $R^1=R^2=R^4=H$, $R^3=Br$
 Meridianin E (5) $R^1=R^2=R^3=H$, $R^4=Br$
 Meridianin F (6) $R^1=R^4=H$, $R^2=R^3=Br$
 Meridianin G (7) $R^1=R^2=R^3=R^4=H$

2. Result and discussion

The retro synthesis of substituted meridianins **5a–d** is shown in Scheme 1. Since monothio-1,3-diketones are potentially useful 3-carbon 1,3-bielectrophilic synthons for the construction of 5- and 6-membered heterocycles (Kumar et al., 2013), we envisaged the cyclocondensation of monothio-1,3-diketone **4** with guanidine. The monothio-1,3-diketone **4** was to be accessed by thioacylation of dithioesters **3** and 3-acetyl indole **1** which was *N*-benzylated.

With ready availability of 3-acetyl indole **1**, straightforward *N*-benzylation with 78% yield was achieved. As per our previous studies (Jenifer Vijay, Nandeesh, Raghavendra, Rangappa, & Mantelingu, 2013), we synthesized monothio-1,3-diketone **4** using simple dithioester **3** in presence of NaH as base and DMF as solvent. The best result with 80% yield was obtained when 2 equivalents of NaH.

Scheme 1. Retro synthesis of meridianin analog.

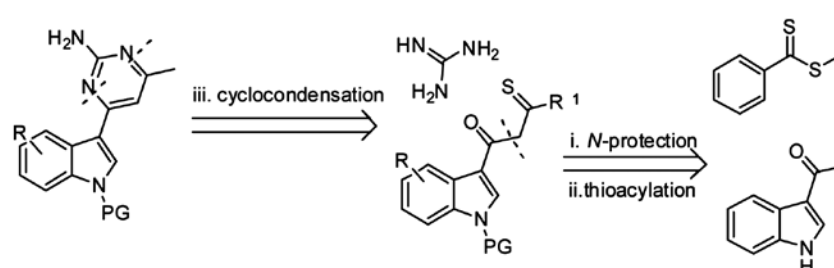
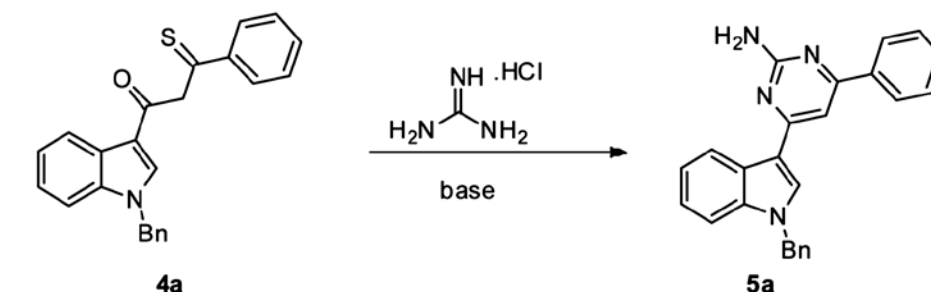


Table 1. Establishment of reaction conditions



Entry	Base ^a	Solvent (mL)	Time (h)	Yield (%) ^b
1	KOH	EtOH	8–10	20
2	NaOH	EtOH	8–10	22
3	<i>t</i> -BuOK	EtOH	8–10	25
4	MeONa	EtOH	8–10	Traces
5	NaH	EtOH	8–10	–
6	NaH	DMF	8–10	–
7	TEA	DMF	8–10	–
8	K ₂ CO ₃ (1 equiv)	EtOH	8–10	53
9	K ₂ CO ₃ (1.5 equiv)	EtOH	7	57
10	K ₂ CO ₃ (2.0 equiv)	EtOH	5	66
11	K ₂ CO ₃ (2.5 equiv)	EtOH	5	71
12	K ₂ CO ₃ (3.0 equiv)	EtOH	5	68

^aThe mixture of **4a** (1.0 mmol), guanidine hydrochloride (1.5 mmol) and 2 equiv base in 5 mL solvent was stirred in a flask at reflux condition.

^bIsolated yield.

Finally, the pivotal step that is, the cyclocondensation of the monothio-1,3-diketone **4** with guanidine under suitable base and solvent was attempted. To start with monothio-1,3-diketone **4a** and guanidine hydrochloride was chosen as template reactants; KOH (1 equiv) were chosen as base and ethanol as solvent, and the reaction was carried out under reflux condition (Table 1, entry 1) resulting in 20% yield.

Encouraged by the result, we tried several bases like, NaOH, KOH, *t*-BuOK, MeONa, TEA, NaH (for solvents EtOH and DMF), and K_2CO_3 (for different equivalences) (Table 1, entries 1–12). As K_2CO_3 provided better results (Table 1, entry 8), its loading was optimized. It was found that 2.5 equiv of K_2CO_3 gave a maximum yield of 71% (Table 1, entry 11), but 3.0 equiv of K_2CO_3 gave slightly decreased yield (Table 1, entry 12). Thus establishing an efficient method with simple work-up was achieved by employing 2.5 equiv of K_2CO_3 in ethanol at refluxing condition. Within 5 h, the products were formed in moderate to good yields as pale yellow solids (Scheme 2).

With the optimized reaction conditions, analog of Meridianin G **5a** was synthesized using guanidine hydrochloride and 1-(1-benzyl-1*H*-indol-3-yl)-3-phenyl-3-thioxopropan-1-one **4a**, which was readily synthesized by thioacylation of 1-(1-benzyl-1*H*-indol-3-yl)ethanone **2a** and phenyldithioester **3a** (Table 2, entry 1). The formation of Meridianin G **5a** was ascertained by characterization data. The 1H NMR of 4-(1-benzyl-1*H*-indol-3-yl)-6-phenylpyrimidin-2-amine **5a** displayed four singlets at δ 7.93 ppm (2-H of indolyl), δ 7.43 ppm (2-aminopyrimidine CH), δ 5.39 ppm (broad singlet of NH_2), and δ 5.19 ppm ($N-CH_2$). A doublet at δ 8.42 ppm correlates to C-4 of indolyl ring and the aromatic protons is indicated by the multiplets at δ 7.51–7.48 ppm and δ 7.36–7.19 ppm. The ^{13}C NMR of **5a** exhibited seventeen signals with indicative signals at δ 106.6 ppm assigned to the CH of 2-aminopyrimidine ring and 50.8 ppm assigned to $N-CH_2$ group. The IR values also indicate the presence of primary amine with N-H stretching frequency at $3,332\text{ cm}^{-1}$ and bending frequency $1,582\text{ cm}^{-1}$. In addition, the mass spectrum and analytical data confirm the structure of **5a**. The results indicated the successful synthesis of **5a**.

Thus, Meridianin G was further varied using 4-methoxyphenyldithioester **3b** (Table 2, entry 2) and 2-thiophenedithioester **3c** (Table 2, entry 3). Meridianin C was also synthesized in a similar way using 1-(1-benzyl-5-bromo-1*H*-indol-3-yl)-3-phenyl-3-thioxopropan-1-one **4d**, which was accessed from 1-(1-benzyl-5-bromo-1*H*-indol-3-yl)ethanone **2d** (Table 2, entry 4). The structures of all the substituted meridianins **4a–d** were characterized by 1H , ^{13}C NMR, and mass spectrometry (see Supplementary material).

It is presumed that the mechanism for cyclocondensation of monothio 1,3-diketones **4** with guanidine is as depicted in Scheme 3. The probable route could be the attack of guanidine on thioenolic form of **4** to give the intermediate **A**. The intermediate **A** on subsequent elimination of mercapto group undergoes intramolecular cyclization with loss of a molecule of water to yield substituted meridianin **5**.

Scheme 2. Facile route for the synthesis of substituted meridianins.

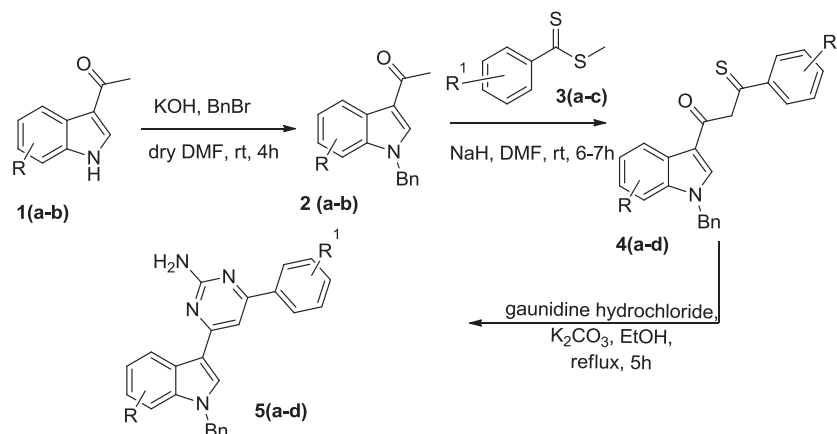
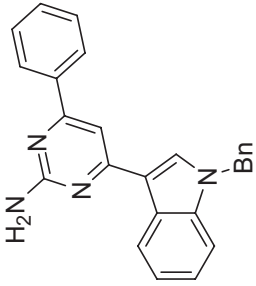
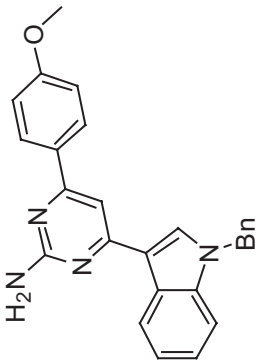
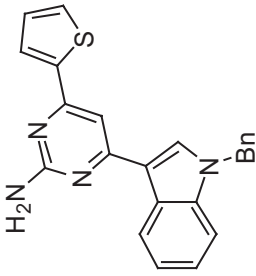
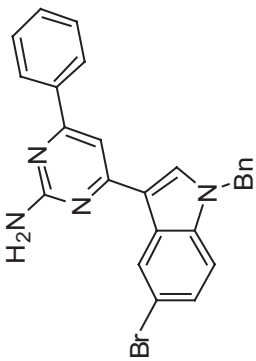


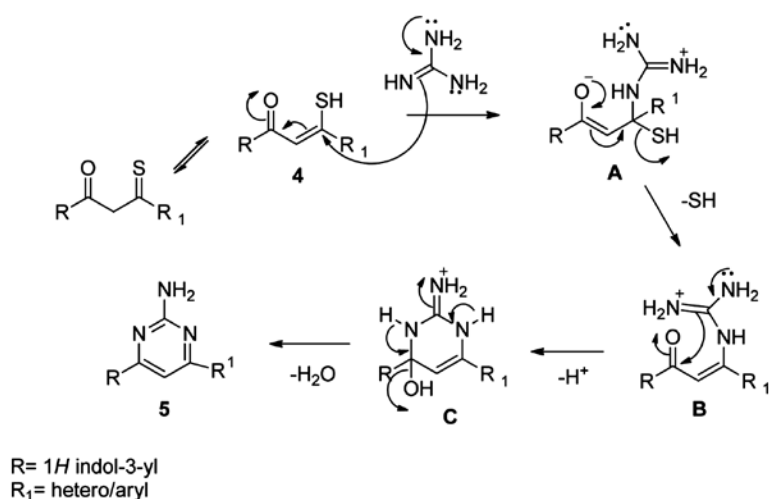
Table 2. Structures of newly synthesized substituted meridianins ^a			
			
5a [71%] ^b	5b [76%] ^c	5c [78%] ^b	5d [68%] ^b

^aGeneral conditions for **5a–d**: **4a** (1.0 mmol), guanidine hydrochloride (1.5 mmol), K₂CO₃ (2.5 mmol) in ethanol, reflux, 5 h.

^bIsolated yield.

^cReported compounds (Yu & Yu, 2009).

Scheme 3. Plausible mechanism for the synthesis of compounds 5(a–d).



3. Experimental

3.1. Preparation of *N*-benzyl-3-acetylindole (Corbel et al., 2007)

A mixture of 3-acetyl indole (2.5 g, 15.72 mmol) and potassium hydroxide (1.25 g, 22.27 mmol) in dry DMF (10 mL) was stirred until solubilization of KOH. Next, benzyl bromide (1.4 mL, 11.77 mmol) was added and stirred at room temperature until 3-acetyl indole disappeared (monitored by TLC). After completion of reaction, the mixture was poured into water and extracted to ethyl acetate, was dried over sodium sulfate. Solvent was removed and half-white solid was recrystallized with diethyl ether.

3.2. Preparation of 1-(1-benzyl-1*H*-indol-3-yl)-3-(het)aryl-3-thioxopropan-1-one derivatives 4(a–d) (Raghava et al., 2014)

To 60% suspension of NaH in mineral oil (0.06 g, 2.5 mmol) in DMF (2 mL) at 0°C was added *N*-benzyl-3-acetylindole (0.249 g, 1.0 mmol) followed by stirring for 10–15 min at room temperature. A solution of dithioester (1.0 mmol) in DMF (2 mL) was added over a period of 10 min at 0°C followed by stirring at room temperature for 6–7 h. The completion of the reaction was monitored by TLC. The mixture was poured into water and extracted with ethyl acetate (2 × 25 mL). The combined organic layer was washed with brine (25 mL) and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the crude product was passed through a small plug of silica using hexane/ethyl acetate (9:1) to afford 1-(1-benzyl-1*H*-indol-3-yl)-3-(het)aryl-3-thioxopropan-1-one derivatives 4(a–d).

3.3. Preparation of substituted meridianin 5(a–d)

Guanidine hydrochloride (0.142 g, 1.5 mmol) was added to a stirred suspension of K₂CO₃ (0.346 g, 2.5 mmol) in EtOH (95%; 10 mL), and then a solution of 1-(1-benzyl-1*H*-indol-3-yl)-3-(het)aryl-3-thioxopropan-1-one (1.0 mmol) in ethanol (2 mL) was added. The reaction mixture was heated at reflux with stirring for 5–6 h (monitored by TLC). The mixture was then filtered over Celite® S and the filtrate was concentrated to dryness under reduced pressure and the residue was extracted with ethyl acetate (2 × 25 mL). The organic phase was washed with water (2 × 25 mL) and brine (25 mL), dried (Na₂SO₄), and concentrated under reduced pressure to get crude products, which were purified by column chromatography on silica gel using hexane/ethyl acetate (7:3) to afford substituted meridianins 5(a–d).

3.3.1. 4-(1-benzyl-1*H*-indol-3-yl)-6-phenylpyrimidin-2-amine (5a)

Following the general procedure, compound 5a was obtained from the reaction between 1-(1-benzyl-1*H*-indol-3-yl)-3-phenyl-3-thioxopropan-1-one (4a) and guanidine hydrochloride as a

cream-colored solid with 71% yield; mp 164–166°C; ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 8.42 (d, J = 8.0 Hz, 1H, aromatic CH), 8.04 (d, J = 7.4 Hz, 2H, aromatic CH), 7.93 (s, 1H, 2-H of indolyl), 7.51–7.47 (m, 3H, aromatic CH), 7.43 (s, 1H, *N*-heteroaryl CH), 7.36–7.19 (m, 6H, aromatic CH), 7.18 (d, J = 6.4 Hz, 2H, aromatic CH), 5.39 (s, 2H, NH_2), 5.19 (s, 2H, *N*- CH_2); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$): δ 164.0, 163.2, 158.3, 137.9, 133.3, 131.1, 129.1, 127.6, 127.4, 126.5, 124.0, 123.0, 121.6, 113.7, 111.0, 106.6 (CH), 50.8 (CH_2); IR (KBr): 3,332, 3,089, 2,955, 2,861, 1,582, 1,505, 1,049, 865, 753 cm^{-1} ; MS (ESI + ion): m/z = 377.2 (M^+). Anal. Calcd for $\text{C}_{25}\text{H}_{20}\text{N}_4$: C, 79.76; H, 5.35; N, 14.88. Found: C, 79.74; H, 5.34; N, 14.87.

3.3.2. 4-(1-benzyl-1*H*-indol-3-yl)-6-(4-methoxyphenyl) pyrimidin-2-amine (Yu & Yu, 2009) (5b)

Following the general procedure, compound **5b** was obtained from the reaction between 1-(1-benzyl-1*H*-indol-3-yl)-3-(4-methoxyphenyl)-3-thioxopropan-1-one (**4b**) and guanidine hydrochloride as a half-white-colored solid with 76% yield; mp 195–196°C; ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 8.43 (d, J = 6.8 Hz, 1H, aromatic CH), 8.05 (d, J = 6.8 Hz, 2H, aromatic CH), 7.94 (s, 1H, 2-H of indolyl), 7.51–7.48 (m, 3H, aromatic CH), 7.44 (s, 1H, *N*-heteroaryl CH), 7.36–7.28 (m, 7H, aromatic CH), 7.19 (d, J = 8.0 Hz, 2H, aromatic CH), 5.40 (s, 2H, NH_2), 5.20 (s, 2H, *N*- CH_2), 3.84 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$): δ 164.1, 164.0, 163.2, 158.3, 136.9, 131.1, 130.1, 128.3, 127.5, 127.4, 126.1, 123.0, 122.0, 120.6, 113.8, 110.0, 100.0 (CH), 55.2 (CH_2), 50.7 (OCH_3); IR (KBr): 3,330, 3,150, 2,595, 2,761, 1,573, 1,604, 1,300, 1,150, 765, 642 cm^{-1} ; MS (ESI + ion): m/z = 407.7 (M^+). Anal. Calcd for $\text{C}_{24}\text{H}_{17}\text{NOS}$: C, 76.83; H, 5.46; N, 13.78. Found: C, 76.81; H, 5.45; N, 13.79.

3.3.3. 4-(1-benzyl-1*H*-indol-3-yl)-6-(thiophen-2-yl)pyrimidin-2-amine (5c)

Following the general procedure, compound **5c** was obtained from the reaction between 1-(1-benzyl-1*H*-indol-3-yl)-3-(thiophen-2-yl)-3-thioxopropan-1-one (**4c**) and guanidine hydrochloride as a pale yellow-colored solid with 78% yield; mp 112–113°C; ^1H NMR (400 MHz, CDCl_3): δ 8.57 (s, 1H, 2-H of indolyl), 7.95 (s, 1H, *N*-heteroaryl CH), 7.81 (d, J = 8.8 Hz, 2H), 7.58 (t, J = 8.4 Hz, 1H), 7.46 (d, J = 8.8 Hz, 4H, aromatic CH), 7.40–7.27 (m, 3H, aromatic CH), 7.25 (d, J = 8.8 Hz, 2H, aromatic CH), 5.61 (s, 2H, NH_2), 5.47 (s, 2H, *N*- CH_2); ^{13}C NMR (100 MHz, CDCl_3): δ 177.5, 176.3, 143.4, 138.3, 136.0, 129.2, 128.8, 128.0, 126.7, 125.7, 122.2, 122.1, 122.0, 112.9, 109.6, 100.1 (CH), 54.1 (CH_2); IR (KBr): 3,335, 3,178, 3,025, 2,671, 1,579, 1,516, 1,053, 887, 731 cm^{-1} ; MS (ESI + ion): m/z = 382.9 (M^+). Anal. Calcd for $\text{C}_{24}\text{H}_{17}\text{NOS}$: C, 72.22; H, 4.74; N, 14.65. Found: C, 72.21; H, 4.73; N, 14.64.

3.3.4. 4-(1-benzyl-5-bromo-1*H*-indol-3-yl)-6-phenylpyrimidin-2-amine (5d)

Following the general procedure, compound **5d** was obtained from the reaction 1-(1-benzyl-5-bromo-1*H*-indol-3-yl)-3-phenyl-3-thioxopropan-1-one (**4d**) and guanidine hydrochloride as a pale brown-colored solid with 68% yield; mp 174–176°C; ^1H NMR (400 MHz, CDCl_3): δ 8.55 (s, 1H, aromatic CH), 8.33 (s, 1H, 2-H of indolyl), 8.20–8.12 (m, 3H, aromatic CH), 8.06 (d, J = 8.0 Hz, 1H, aromatic CH next to Br), 7.75–7.71 (m, 2H, aromatic CH, *N*-heteroaryl CH), 7.66 (d, J = 7.2 Hz, 1H, aromatic CH), 7.33–7.30 (m, 4H, aromatic CH), 7.14–7.10 (m, 2H, aromatic CH), 5.51 (s, 2H, NH_2), 5.31 (s, 2H, *N*- CH_2); ^{13}C NMR (100 MHz, CDCl_3): δ 163.8, 162.8, 162.7, 161.0, 137.3, 135.6, 133.1, 130.0, 128.2, 127.7, 127.1, 125.0, 124.8, 114.9, 113.5, 112.6, 100.2 (CH), 55.3 (CH_2); IR (KBr): 3,334, 3,109, 2,975, 2,851, 1,578, 1,512, 1,052, 799, 733, 510 cm^{-1} ; MS (ESI + ion): m/z = 456.8 (M^+). Anal. Calcd for $\text{C}_{24}\text{H}_{17}\text{NOS}$: C, 65.94; H, 4.21; N, 12.30; Found: C, 65.93; H, 4.18; N, 12.29.

4. Conclusion

In conclusion, we have devised an efficient method for the synthesis of substituted meridianins, especially Meridianin C and Meridianin G. Unlike the earlier reports, our method does not involve the use of transition metal catalysts and drastic conditions. The reaction was reduced to a three-step procedure using readily available reactants. In addition, this method provides a scope to synthesize various derivatives whilst the formation of the final product. As a result, it provides a large spectrum of compounds for biological screening.

Supplementary material

Supplementary material for this article can be accessed here <http://dx.doi.org/10.1080/23312009.2015.1083068>.

Acknowledgements

The Ministry of Human-Resource Development (MHRD) and University Grant Commission (UGC), New Delhi, India, are acknowledged for recognizing University of Mysore as the Institute of Excellence and for the fellowship. We also thank NMR Facility, IOE, University of Mysore, Manasagangotri, Mysore 570 006, India, for spectral data.

Funding

The authors received no direct funding for this research.

Competing interests

The author(s) confirm that the above content has no "Competing Interests".

Author details

Jenifer T.A. Vijay¹
 E-mail: jenny.sonia05@gmail.com
 Nandeesh K. Nagalingaiah¹
 E-mail: nandeesh.nagalingaiah@gmail.com
 Sandhya C. Nagarakere¹
 E-mail: sandhyamaddur@gmail.com
 G.P. Suresha¹
 E-mail: suri_gp@yahoo.com
 ORCID ID: <http://orcid.org/0000-0002-3445-2369>
 Rangappa S. Kanchugarakoppal¹
 E-mail: rangappaks@gmail.com
 Mantelingu Kempegowda¹
 E-mail: kmantelingu@yahoo.com

¹ Department of Studies in Chemistry, Manasagangotri, University of Mysore, Mysore 570006, India.

Citation information

Cite this article as: Concise synthesis of substituted meridianins, Jenifer T.A. Vijay, Nandeesh K. Nagalingaiah, Sandhya C. Nagarakere, G.P. Suresha, Rangappa S. Kanchugarakoppal & Mantelingu Kempegowda, *Cogent Chemistry* (2015), 1: 1083068.

Cover image

Source: Authors.

References

- Agarwal, P. K., Dathi, M. D., Saifuddin, M., & Kundu, B. (2012). Engineering of indole-based tethered biheterocyclic alkaloid meridianin into β -carboline-derived tetracyclic polyheterocycles via amino functionalization/6-endo cationic π -cyclization. *Beilstein Journal of Organic Chemistry*, 8, 1901–1908. doi:10.3762/bjoc.8.220
- Akue-Gedu, R., Debiton, E., Ferandin, Y., Meijer, L., Prudhomme, M., Anizon, F., & Moreau, P. (2009). Synthesis and biological activities of aminopyrimidyl-indoles structurally related to meridianins. *Bioorganic & Medicinal Chemistry*, 17, 4420–4424. doi:10.1016/j.bmc.2009.05.017
- Bharate, S. B., Yadav, R. R., Battula, S., & Vishwakarma, R. A. (2012). Meridianins: Marine-derived potent kinase inhibitors. *Mini Reviews in Medicinal Chemistry*, 12, 618–631. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/22512550>
<http://dx.doi.org/10.2174/138955712800626728>
- Butler, M., Capon, R., & Lu, C. (1992). Psammopemmins (A–C), novel brominated 4-hydroxyindole alkaloids from an antarctic sponge, Psammopemma sp. *Australian Journal of Chemistry*, 45, 1871–1877. doi:10.1071/CH9921871
- Corbel, B., Michaud, F., Meijer, L., Simon, G., Couthon-Gourves, H., Haelters, J.-P., & Kervarec, N. (2007). Towards the syntheses of N–H and N-alkylated derivatives of meridianins. *Journal of Heterocyclic Chemistry*, 44, 793–801. doi:10.1002/jhet.5570440407
- Endo, T., Tsuda, M., Fromont, J., & Kobayashi, J. (2007). Hyrtinadine A, a bis-indole alkaloid from a marine sponge. *Journal of Natural Products*, 70, 423–424. doi:10.1021/np060420n
- Fresneda, P. M., Molina, P., & Bleda, J. A. (2001). Synthesis of the indole alkaloids meridianins from the tunicate *Aplidium meridianum*. *Tetrahedron*, 57, 2355–2363. [http://dx.doi.org/10.1016/S0040-4020\(01\)00102-8](http://dx.doi.org/10.1016/S0040-4020(01)00102-8)
- Fresneda, P. M., Molina, P., Delgado, S., & Bleda, J. A. (2000). Synthetic studies towards the 2-aminopyrimidine alkaloids variolins and meridianins from marine origin. *Tetrahedron Letters*, 41, 4777–4780. [http://dx.doi.org/10.1016/S0040-4039\(00\)00728-0](http://dx.doi.org/10.1016/S0040-4039(00)00728-0)
- Gompel, M., Leost, M., De Kier Joffe, E. B., Puricelli, L., Franco, L. H., Palermo, J., & Meijer, L. (2004). Meridianins, a new family of protein kinase inhibitors isolated from the ascidian *Aplidium meridianum*. *Bioorganic & Medicinal Chemistry Letters*, 14, 1703–1707. doi:10.1016/j.bmcl.2004.01.050
- Herna, L., Bal, E., Joffe, D. K., Puricelli, L., Tatian, M., Seldes, A. M., & Palermo, J. A. (1998). Indole alkaloids from the tunicate *Aplidium meridianum*. *Journal of Natural Products*, 61, 1130–1132.
- Jenifer Vijay, T. A., Nandeesh, K. N., Raghavendra, G. M., Rangappa, K. S., & Mantelingu, K. (2013). Transition metal free intramolecular S-arylation: One-pot synthesis of thiochromen-4-ones. *Tetrahedron Letters*, 54, 6533–6537. doi:10.1016/j.tetlet.2013.09.094
- Jiang, B., & Yang, C. (2000). Synthesis of indolylpyrimidines via cross-coupling of indolylboronic acid with chloropyrimidines: Facile synthesis of meridianin D. *Heterocycles*, 53, 1489–1498. doi:10.3987/COM-00-8890
- Karpov, A. S., Merkul, E., Rominger, F., & Müller, T. J. J. (2005). Concise syntheses of meridianins by carbonylative alkynylation and a four-component pyrimidine synthesis. *Angewandte Chemie International Edition*, 44, 6951–6956. doi:10.1002/anie.200501703
- Kumar, S. V., Yadav, S. K., Raghava, B., Saraiha, B., Ila, H., Rangappa, K. S., & Hazra, A. (2013). Cyclocondensation of arylhydrazines with 1,3-bis(het)arylmonothio-1,3-diketones and 1,3-bis(het)aryl-3-(methylthio)-2-propenones: Synthesis of 1-aryl-3,5-bis(het)arylpyrazoles with complementary regioselectivity. *The Journal of Organic Chemistry*, 78, 4960–4973. doi:10.1021/jo400599e
- More, K. N., Jang, H. W., Hong, V. S., & Lee, J. (2014). Pim kinase inhibitory and antiproliferative activity of a novel series of Meridianin C derivatives. *Bioorganic & Medicinal Chemistry Letters*, 24, 2424–2428. doi:10.1016/j.bmcl.2014.04.035
- Raghava, B., Parameshwarappa, G., Acharya, A., Swaroop, T. R., Rangappa, K. S., & Ila, H. (2014). Cyclocondensation of hydroxylamine with 1,3-bis(het)arylmonothio 1,3-diketones and 1,3-bis(het)aryl-3-(methylthio)-2-propenones: Synthesis of 3,5-bis(het)arylisoxazoles with complementary regioselectivity. *European Journal of Organic Chemistry*, 2014, 1882–1892. doi:10.1002/ejoc.201301667
- Reyes, F., Fernández, R., Rodríguez, A., Francesch, A., Taboada, S., Ávila, C., & Cuevas, C. (2008). Aplicyanins A–F, new cytotoxic bromindole derivatives from the marine tunicate *Aplidium cyaneum*. *Tetrahedron*, 64, 5119–5123. doi:10.1016/j.tet.2008.03.060
- Seldes, a. M., Rodríguez Brasco, M. F. R., Hernandez Franco, L. H., & Palermo, J. a. (2007). Identification of two meridianins from the crude extract of the tunicate *Aplidium meridianum* by tandem mass spectrometry. *Natural Product Research*, 21, 555–563. doi:10.1080/14786410601133517

- Sperry, J. (2011). A concise synthesis of meridianin F. *Tetrahedron Letters*, 52, 4537–4538. doi:10.1016/j.tetlet.2011.06.073
- Sundberg, R. J. (2010). *Heterocyclic scaffolds II: Topics in heterocyclic chemistry*. (G. W. Gribble, Ed.) (Vol. 26, pp. 47–115). Berlin, Heidelberg: Springer Berlin Heidelberg. doi:10.1007/978-3-642-15733-2
- Tibiletti, F., Simonetti, M., Nicholas, K. M., Palmisano, G., Parravicini, M., Imbesi, F., ... Penoni, A. (2010). One-pot synthesis of meridianins and meridianin analogues via indolization of nitrosoarenes. *Tetrahedron*, 66, 1280–1288. doi:10.1016/j.tet.2009.12.020
- Trimurtulu, G., Faulkner, D. J., Perry, N. B., Ettouati, L., Litaudon, M., Blunt, J. W., ... Munro, M. H. G. (1994). Alkaloids from the antarctic sponge *Kirkpatrickia variolosa*. Part 2: Variolin A and N(3')-methyl tetrahydrovariolin B. *Tetrahedron*, 50, 3993–4000. doi:10.1016/S0040-4020(01)89674-5
- Walker, S. R., Czyz, M. L., & Morris, J. C. (2014). Concise syntheses of meridianins and meriolins using a catalytic domino amino–palladation reaction. *Organic Letters*, 16, 708–711. doi:10.1021/ol403390m
- Yu, H., & Yu, Z. (2009). Direct alkenylation of indoles with α -oxo ketene dithioacetals: Efficient synthesis of indole alkaloids meridianin derivatives. *Angewandte Chemie International Edition*, 48, 2929–2933. doi:10.1002/anie.200900278



© 2015 The Author(s). This open access article is distributed under a Creative Commons Attribution (CC-BY) 4.0 license.

You are free to:

Share — copy and redistribute the material in any medium or format

Adapt — remix, transform, and build upon the material for any purpose, even commercially.

The licensor cannot revoke these freedoms as long as you follow the license terms.

Under the following terms:

Attribution — You must give appropriate credit, provide a link to the license, and indicate if changes were made.

You may do so in any reasonable manner, but not in any way that suggests the licensor endorses you or your use.

No additional restrictions

You may not apply legal terms or technological measures that legally restrict others from doing anything the license permits.



Cogent Chemistry (ISSN: 2331-2009) is published by Cogent OA, part of Taylor & Francis Group.

Publishing with Cogent OA ensures:

- Immediate, universal access to your article on publication
- High visibility and discoverability via the Cogent OA website as well as Taylor & Francis Online
- Download and citation statistics for your article
- Rapid online publication
- Input from, and dialog with, expert editors and editorial boards
- Retention of full copyright of your article
- Guaranteed legacy preservation of your article
- Discounts and waivers for authors in developing regions

Submit your manuscript to a Cogent OA journal at www.CogentOA.com

